Relationships among Nutrition, Gestational Development, & Chiari

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Importance for Chiari patients

Nutrient, genetic, and environmental factors influence gestational development. Over or under exposure to any of these components contribute to the risk for congenital malformations (e.g. spina bifida & folic acid). We aim to develop a plan to explore the relations between these factors and the risk for developing Chiari. If successfully identified, we would be able to design targeted interventions to reduce incidence of Chiari.

Importance of Nutrients in Chiari Risk

Complex interactions among nutrition, genetics, and environmental exposures may influence the risk for developing Chiari (Figure 1). Polymorphisms (variation) in genes involved in nutrient metabolism influence individual nutrient requirements of some dietary components. Adequate amounts of vitamin A, folate, and choline, for example, are required for gestational development. This includes formation of the neural tube, cranium, eyes, other facial structures, and cerebellum (structural and cognitive). Many women, however, do not know they are pregnant until after the first month of embryonic development. During the first four weeks of gestation, structures such as the neural tube develop.

Investigating the role of nutrition as it relates to the risk for developing Chiari involves assessing current and past nutritional intakes, determining whether or not a pattern exists with regard to variation in genes involved in the metabolism of key dietary components evidenced to play a relevant role in gestational development, and assessing environmental factors that may interact with diet to contribute to the risk of developing Chiari.

The following factors are of interest 1) Vitamin A, 2) methyl donors and 3) medical history and environmental exposures.

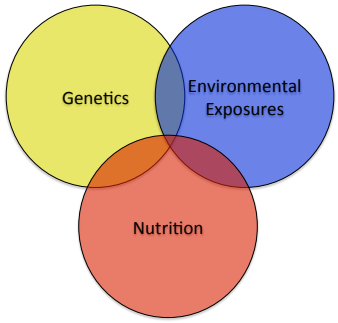

Figure 1. Interaction of factors that could increase risk for Chiari

Vitamin A

The timing, dose (concentration), and duration of exposure to vitamin A , predominately as retinoic acid, guides many aspects of gestational development. Too little or too much irrevocably disrupts the process. The following aspects of vitamin A metabolism with regard to risk for developing Chiari can be targeted for analysis:

- Retinal dehydrogenase enzymes (ALDH) metabolize vitamin A (retinal) to retinoic acid. ALDH isoforms have been investigated with regard to the risk of developing a neural tube defect and other malformations.
- Cytochrome P450 (CYP26B1 and CYP26A1) enzymes control the amount of active vs. inactive retinoic acid available in the body. Different forms of these enzymes are expressed depending on the tissue.
- Stimulated by retinoic acid gene 6 homolog (STRA6) is a membrane protein that binds to metabolized vitamin A which circulates in the blood as retinol. STRA6 genetic mutations have been associated with micropthalmia, anopthalmia, cardiac defects, and craniofacial abnormalities.

Methyl Donors

Folate, vitamin B12, and choline contribute to the availability of methyl groups. A deficiency of any of these nutrients, a SNP in a gene involved in the metabolism of these nutrients, or a combination of these alters availability of methyl groups throughout the body. This in turn may impact gene expression through altering DNA methylation and other epigenetic effects.

Proposed Methods

This study would entail a two tiered approach: Part I) Identify polymorphisms in enzymes that metabolize the nutrients described above in a diverse group of Chiari patients and family members and Part II) determine if the polymorphisms are present in a group of pregnant women with family history of Chiari and if those are heritable traits passed on to their children.

The following assessments would be considered for the study:

- **Diet Analysis:** Food frequency questionnaires, diet histories (3-day diet records and/or 24-hour diet recall); supplement use
- **Blood collection:** Analysis of blood for vitamin A, vitamin B12, folate, and choline status; DNA analysis for presence of SNPs in genes related to metabolism of these nutrients
- **Anthropometric data:** height, weight, BMI calculations; pre- and post pregnancy weight
- **Environment:** Zipcode data; potential survey questions (age of home, lead paint exposure, etc.)
- **Medical history:** family history of Chiari, neural tube defects, other congenital malformations; point at which (wk gestation) pregnancy identified; prenatal care; use of prenatal supplements; family history. Medical record access may be requested.

Limitations

This type of study may require a large sample size. Another challenge is that Chiari symptomatology can manifest late in life. Thus, a longitudinal study may be required over a long time period. Dietary intake data can be difficult to obtain and required a high degree of participation. In part II a blood sample will be needed from pregnant women and then their children.

Potential Impact

If successful, this study would be able to help design individualized preventative plans for people at risk for Chiari. The results would also help increase fundamental understanding of the complex interplay of genetic, environment, and nutrition in development of neurological disorders related with Chiari.